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REVIEW ARTICLE

Cardiorenal syndrome: clinical diagnosis, molecular mechanisms and therapeutic strategies

Bo-rui Zhao[1,2], Xin-rong Hu[1,3], Wei-dong Wang[4,5] and Yi Zhou[1,3]✉

As the heart and kidneys are closely connected by the circulatory system, primary dysfunction of either organ usually leads to secondary dysfunction or damage to the other organ. These interactions play a major role in the pathogenesis of a clinical entity named cardiorenal syndrome (CRS). The pathophysiology of CRS is complicated and involves multiple body systems. In early studies, CRS was classified into five subtypes according to the organs associated with the vicious cycle and the acuteness and chronicity of CRS. Increasing evidence shows that CRS is associated with a variety of pathological mechanisms, such as haemodynamics, neurohormonal changes, hypervolemia, hypertension, hyperuraemia and hyperuricaemia. In this review, we summarize the classification and currently available diagnostic biomarkers of CRS. We highlight the recently revealed molecular pathogenesis of CRS, such as oxidative stress and inflammation, hyperactive renin–angiotensin–aldosterone system, maladaptive Wnt/β-catenin signalling pathway and profibrotic TGF–β1/Smad signalling pathway, as well as other pathogeneses, such as dysbiosis of the gut microbiota and dysregulation of noncoding RNAs. Targeting these CRS-associated signalling pathways has new therapeutic potential for treating CRS. In addition, various chemical drugs, natural products, complementary therapies, blockers, and agonists that protect against CRS are summarized. Since the molecular mechanisms of CRS remain to be elucidated, no single intervention has been shown to be effective in treating CRS. Pharmacologic therapies designed to block CRS are urgently needed. This review presents a critical therapeutic avenue for targeting CRS and concurrently illuminates challenges and opportunities for discovering novel treatment strategies for CRS.

Keywords: cardiorenal syndrome; oxidative stress and inflammation; renin–angiotensin–aldosterone system; TGF-β1/Smad; gut microbiota; noncoding RNAs

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INTRODUCTION

As the heart and kidneys are closely connected by the circulatory system, primary dysfunction of either organ usually leads to secondary dysfunction or damage to the other organ [1–3]. These interactions potentially play a role in the pathogenesis of a clinical entity named cardiorenal syndrome (CRS). CRS leads to a broad spectrum of acute and chronic diseases, such as acute heart failure (AHF), acute kidney injury (AKI), chronic heart failure (CHF) and chronic kidney disease (CKD) [1, 4]. CRS is associated with high morbidity and mortality in patients. CRS accounts for approximately 33% of acute decompensated cardiac failure admissions, and patients with continuous congestion at discharge have high 30-day event rates [5]. More than 60% of patients admitted for acute decompensated heart failure suffer from CKD. CKD, in turn, is one of the most important risk factors for mortality and cardiovascular disease (CVD) in patients with acute decompensated heart failure [6–8]. Moreover, even a slight decrease in kidney function is related to a high death rate in CVD patients [9, 10]. The latest report revealed that middle-aged and older adults with type 1 diabetes experienced a higher risk of CRS than those with type 2 diabetes [11]. Based on the acuteness and chronicity of the disease, CRS is systematically classified into 5 different categories to provide a more precise strategy for clinical diagnosis [3, 4, 12]. Physicians often experience diagnostic and therapeutic challenges in patient management because of the enigmatic pathophysiological mechanisms, lack of clinical diagnostic tools and individual biases [2, 13]. However, biomarkers provide an early diagnosis of CRS for timely treatment. Biomarkers can be classified as cardiac functional markers (natriuretic peptides) or renal functional markers (creatinine and cystatin C) [14]. This review presents the clinical diagnosis, highlights the recent underlying molecular mechanism and discusses treatment approaches for CRS.

The reported underlying mechanisms of CRS are associated with venous congestion, arterial underfilling, haemodynamics, neurohormonal activation, oxidative stress and inflammation, and aberrant endothelial function [8]. This review summarises diagnostic biomarkers and the underlying molecular mechanisms,

[1]Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China; [2]Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou 510080, China; [3]NHC Key Laboratory of Clinical Nephrology (Sun Yat-sen University) and Guangdong Provincial Key Laboratory of Nephrology, Guangzhou 510080, China; [4]Institute of Hypertension, Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou 510080, China and [5]Department of Pathophysiology, Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou 510080, China
Correspondence: Yi Zhou (zhouyi39@mail.sysu.edu.cn)
These authors contributed equally: Bo-rui Zhao, Xin-rong Hu

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Table 1. Classification of CRS based on the disease severity and multiple organ systems.

Subtype	Terminology	Outline
CRS1	Acute CRS	Acute cardiac function decline leading to AKI.
CRS2	Chronic CRS	Progressive CKD resulting from chronic cardiac dysfunction.
CRS3	Acute renocardiac syndrome	Sudden and primary deterioration of renal function causing acute cardiac dysfunction.
CRS4	Chronic renocardiac syndrome	Primary CKD leading to impaired cardiac function, ventricular hypertrophy, diastolic aberrant function and elevating cardiovascular risk.
CRS5	Secondary CRS	Acute or chronic systemic disorders leading to concurrent cardiac and renal dysfunction.

such as a hyperactive inhibitor of kappa B (IκB)/nuclear factor kappa B (NF-κB) signalling, impaired Kelch-like ECH-associated protein-1 (Keap1)/nuclear factor-erythroid-2-related factor 2 (Nrf2) signalling, hyperactive renin–angiotensin–aldosterone system (RAAS), maladaptive Wnt/β-catenin and profibrotic transforming growth factor beta 1 (TGF-β1)/small mothers against decapentaplegic (Smad) signalling pathways, as well as dysbiosis of the gut microbiota and dysregulation of noncoding RNAs, of CRS. Moreover, treatments for CRS involving the use of chemical drugs, natural products and complementary therapies are presented. These signalling pathways should be considered as potential therapeutic approaches for CRS treatment.

CLINICAL CLASSIFICATION AND DIAGNOSIS OF CRS

CRS classification

In 2004, the initial definition of CRS was proposed by the Working Group of the National Heart, Lung, and Blood Institute, in which CRS was described as a disease outcome in which the kidneys interact with the remote heart, resulting in an increased circulation volume, deteriorating heart failure and disease development and progression [15]. The Acute Dialysis Quality Initiative introduced a consensus approach that divides CRS into two main groups to further understand the clinical symptoms, disease diagnosis and treatment: cardiorenal and renocardiac syndromes [16]. More specifically, this classification was categorised into five subtypes based on the disease severity and progressive involvement of multiple organ systems [14, 16] (Table 1).

Diagnostic biomarkers of CRS

CRS is a typical disease in which acute or chronic dysfunction of one organ induces acute or chronic damage to another. The available biomarkers that are currently studied and used to diagnose CRS are combinations of markers of AKI or CKD and AHF or CHF, which are also known as multimarker approaches. Therefore, the biomarkers used are classified into different subtypes according to the acute or chronic nature of heart failure and kidney disease.

In CRS1 and CRS3, which combine AKI and AHF, traditional biomarkers of AKI, including creatinine, kidney injury molecule-1 (KIM-1), N-acetyl-*β*-D-glucosaminidase and interleukin (IL)-18, as well as novel renal biomarkers, including cystatin C and neutrophil gelatinase-associated lipocalin (NGAL), are combined with traditional cardiac biomarkers, including cardiac troponin T, B-type natriuretic peptide, N-terminal pro B-type natriuretic peptide (NT-proBNP), myeloperoxidase and midregional proadrenomedullin, as well as novel cardiac biomarkers, such as galectin-3, for diagnosis [15, 17, 18]. Moreover, developing a nomogram for predicting CRS3 in AKI patients enhances early risk prediction and patient management [19]. Traditional and novel biomarkers for CKD, such as creatinine, microalbuminuria, cystatin C, C-reactive protein, homocysteine, uric acid, urotensin II and aldosterone, have been combined with cardiac biomarkers, such as B-type natriuretic peptide, NT-proBNP, C-reactive protein and soluble suppression of tumorigenesis-2 (ST2), to construct a biomarker system for CRS2 and CRS4 [15, 20, 21]. In addition, the diagnosis of CRS5 also relies on the combination of cardiac biomarkers such as B-type natriuretic peptide, C-reactive protein, procalcitonin, and ST2 and renal biomarkers such as creatinine, NGAL, IL-18, KIM-1 and N-acetyl-*β*-D-glucosaminidase [15, 20]. The latest analysis revealed a negative correlation between the CRS risk and the C-reactive protein–albumin–lymphocyte index. This index could be an independent predictor of CRS, outperforming classical inflammatory biomarkers [22]. Recent evidence has shown that trimethylamine N-oxide (TMAO) is an independent risk factor for CVD and all-cause mortality [23]. Furthermore, TMAO was shown to be a mediator of cardiovascular complications in CKD patients [24]. In addition, elevated serum TMAO levels are an independent risk factor for hospitalisation events in patients on haemodialysis [25, 26]. Proteomic techniques have also been used to identify novel biomarkers, such as advanced glycosylation product-specific receptors, periostin and caveolin-1, for the early detection of CRS [27, 28]. Owing to the limitations of combined biomarkers, novel and more accurate biomarkers must be identified in the future to aid in the clinical diagnosis of CRS.

THE UNDERLYING MOLECULAR MECHANISM OF CRS

Previous studies of the underlying mechanisms of CRS have focused mainly on haemodynamics, arterial underfilling, venous congestion, endothelial dysfunction, inflammation and neurohormonal activation. This review highlights novel pathogenic molecular mechanisms of CRS, such as the activation of oxidative stress, inflammation, the RAAS, the maladaptive Wnt/β-catenin signalling pathway and the profibrotic TGF-β1/Smad signalling pathway, and provides new insights into other molecular mechanisms, including dysbiosis of the gut microbiota and dysregulation of noncoding RNAs, in CRS (Figs. 1–4 and Table 2).

Oxidative stress and inflammation in CRS

Oxidative stress and inflammation are independently connected, as they form a vicious cycle in which oxidative stress elicits inflammation through several underlying molecular mechanisms, such as the activation of NF-κB, which results in the activation and recruitment of immune cells [29–31] (Fig. 1). Inflammation, in turn, triggers oxidative stress through the production of reactive oxygen species (ROS) and reactive nitrogen and halogen species derived from activated resident cells and leucocytes. As a result, these processes accelerate organ lesions by inducing apoptosis, necrosis and fibrosis [32]. Under physiological conditions, oxidative stress increases the levels of antioxidants, cytoprotective enzymes and proteins to reduce organ damage. This process is elicited by activated Nrf2, which modulates basal activity and the coordinated induction of the expression of many genes that encode a myriad of antioxidant and phase 2 detoxifying enzymes and associated proteins, such as haem oxygenase-1 (HO-1), catalase, manganese superoxide dismutase (MnSOD), glutamate-cysteine ligase catalytic subunit (GCLC), glutamate-cysteine ligase modifier subunit (GCLM) and nicotinamide adenine dinucleotide phosphate quinone dehydrogenase 1 (NQO1) [33] (Fig. 1).

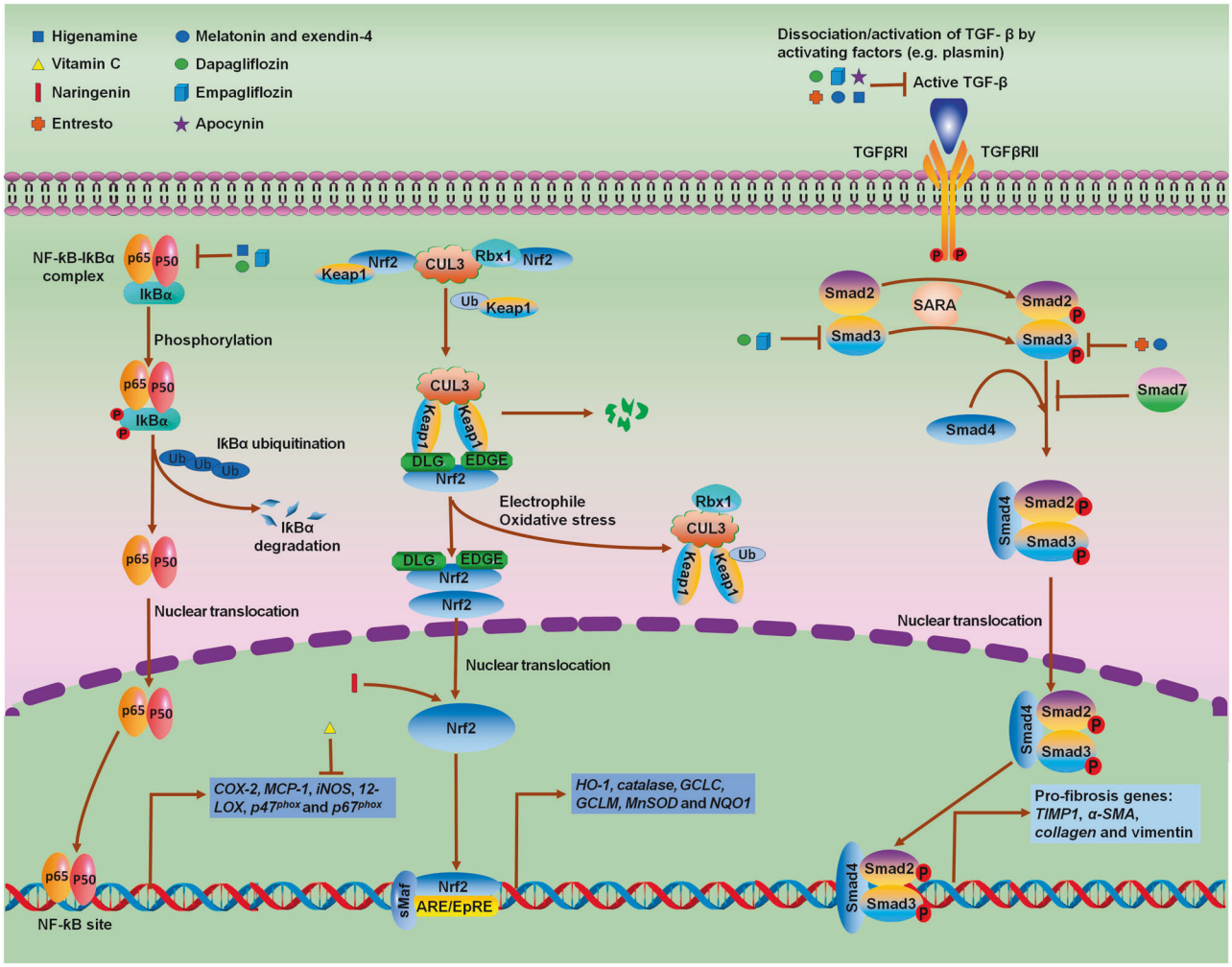

Fig. 1 Targeting the proinflammatory IκB/NF-κB signalling pathway, anti-inflammatory Keap1/Nrf2 signalling pathway and profibrotic TGF-β1/Smad signalling pathway is an important approach for the treatment of CRS. The activation of the IκB/NF-κB and TGF-β1/Smad pathways and the impairment of the Keap1/Nrf2 pathway have been observed in CRS patients, animal models and cell models. Treatment with higenamine, dapagliflozin, empagliflozin and vitamin C improves cardiorenal function by inhibiting the proinflammatory IκB/NF-κB pathways, whereas treatment with naringenin has the same effect on preserving the Keap1/Nrf2 pathway. Moreover, treatment with dapagliflozin, empagliflozin and apocynin ameliorates CRS through the inhibition of the profibrotic TGF-β1/Smad pathway. Therefore, suppressing oxidative stress and inflammation has potential therapeutic effects on CRS.

Substantial evidence suggests that oxidative stress and inflammation play essential roles in the pathogenesis and progression of CRS [34].

Oxidative stress and inflammation in CRS1. CRS1 indicates a state in which AKI occurs in the setting of AHF. The activation of the proinflammatory IκB/NF-κB pathway plays a critical role in oxidative stress and inflammation. NF-κB p65, an important transcription factor, can transcribe a wide range of downstream target genes, such as 12-lipoxygenase (12-LOX), cyclooxygenase-2 (COX-2), monocyte chemotactic protein-1 (MCP-1), inducible nitric oxide synthase (iNOS), $p22^{phox}$, $p47^{phox}$ and $gp91^{phox}$ (Fig. 1). Cho et al. established a CRS rat model by myocardial infarction (MI) using the ligation of the left coronary artery, a low-salt diet and furosemide injection [35]. The model presented an increase in the number of CC chemokine receptor 2^{+} ED-1^{+} monocytes in peripheral blood, accompanied by increased numbers of ED-1^{+} macrophages and increased NF-κB p65 expression in the kidneys of MI model rats, indicating the activation of inflammation in CRS1. Moreover, the intrarenal mRNA expression of *IL-6* and *tumour necrosis factor-alpha* (*TNF-α*) is increased in MI rats [35]. A recent publication revealed that the circulatory system and kidneys of mice with CRS1 presented increased levels of the phosphorylated NF-κB proteins, which was accompanied by increased expression of the MCP-1 and TNF-α proteins [36].

Isoproterenol-induced AHF is a useful reversible model of CRS1. Johnson et al. observed an increase in the mRNA expression of *NGAL*, *HO-1*, *IL-6* and *MCP-1*, which was accompanied by decreased intrarenal glutathione levels and increased malondialdehyde (MDA) levels in the renal tissues of mice with CRS1 [37]. Additionally, increased expression of the MCP-1, IL-6 and HO-1 proteins was observed in the cardiac tissues of mice with isoproterenol-induced AHF [37]. Additionally, angiotensin II (Ang II)-induced human renal glomerular endothelial cells exhibited upregulated expression of the phosphorylated NF-κB, MCP-1, TNF-α, intercellular adhesion molecule-1 (ICAM-1) and vascular intercellular adhesion molecule-1 (VCAM-1) proteins [36]. Taken together, the activation of NF-κB and impairment of Nrf2 signalling pathways are associated with CRS1.

Oxidative stress and inflammation in CRS2. CRS2 is a progressive form of CKD resulting from chronic cardiac dysfunction. Deng et al. established CRS2 rats via left-anterior descending-coronary artery-ligation combined with 5/6 nephrectomy (NX). This model

Table 2. The subtype, pathways, underlying molecular mechanism and targets of CRS.

Patients/animals/cells	Subtype	Pathways	Molecular mechanism and targets	Ref
MI-induced rats	CRS1	Inflammation	Upregulating protein expression of NF-κB p65 and increasing mRNA expression of *IL-6* and *TNF-α*.	[35]
MI-induced rats	CRS1	IκB/NF-κB	Upregulating protein expression of p-NF-κB, MCP-1 and TNF-α.	[36]
Ang II-induced HRGEC	CRS1	IκB/NF-κB	Upregulating protein expression of p-NF-κB, MCP-1, TNF-α, ICAM-1 and VCAM-1.	[36]
Isoproterenol-induced mice	CRS1	IκB/NF-κB and Keap1/Nrf2	Increasing MDA levels, decreasing glutathione levels and upregulating mRNA expression of *NGAL*, *HO-1*, *IL-6* and *MCP-1*.	[37]
LACAL and NX-induced rats and myocyte cells	CRS2	IκB/NF-κB	Upregulating protein expression of p-ASK1 and NF-κB.	[38]
NX and MI-induced rats	CRS2	Inflammation	Increasing $CD3^+$ and $CD68^+$ immune cells.	[39]
Dilated cardiomyopathy mice	CRS2	Keap1/Nrf2	Decreasing renal oxidised glutathione levels.	[40]
Unilateral renal IRI-induced mice	CRS3	IκB/NF-κB	Upregulating iNOS protein expression.	[42]
Unilateral renal IRI-induced mice	CRS3	IκB/NF-κB and Keap1/Nrf2	Increasing activity of SOD, NOX and nitric oxide synthase.	[43]
129 adults	CRS4	Inflammation	Changing levels of TNF-α, IL-6 and hs-CRP.	[44]
Lipopolysaccharide-induced mice	CRS5	IκB/NF-κB and Keap1/Nrf2	Increasing levels of IL-1, IL-6 and TNF-α and decreasing IL-10 levels in serum and heart. Increasing heart levels of MDA, ROS, glutathione peroxidase and SOD.	[46]
CKD patients with CVD	CRS	Inflammation	Increasing serum levels of pentraxin 3, hs-CRP and TNF-α.	[47]
Dahl salt-sensitive rats	CRS	IκB/NF-κB and Keap1/Nrf2	Upregulating protein expression of NF-κB, NOX2 and NOX4 and downregulating protein expression of Nrf2, MnSOD and catalase.	[48]
NX and doxorubicin-induced rats	CRS	IκB/NF-κB	Upregulating protein expression of TNF-α, NF-κB, MMP-2, MMP-9, IL-1β, NOX1, NOX2, NOX4 and their oxidised proteins.	[49]
Doxorubicin/p-cresol-treated H9c2 cells	CRS	IκB/NF-κB	Upregulating protein expression of NOX1, NOX2 and their oxidised proteins.	[49]
NX and doxorubicin-induced rats	CRS	IκB/NF-κB	Upregulating protein expression of TNF-α, NF-κB, MMP-9, iNOS, NOX1, NOX2, NOX4 and their oxidised proteins.	[50]
MI-induced rats	CRS	IκB/NF-κB	Upregulating iNOS protein expression.	[51]
ISCS-induced neonatal rat cardiac myocytes and fibroblasts	CRS	IκB/NF-κB	Upregulating protein expression of ASK1, mitogen-activated protein kinases and NF-κB.	[52]
NX and doxorubicin-induced rats	CRS	IκB/NF-κB	Upregulating protein expression of NOX4, $p22^{phox}$, $p47^{phox}$ and $gp91^{phox}$.	[53]
NX and MI-induced mice and DOCA-induced mice	CRS	IκB/NF-κB	Upregulating MCP-1 protein expression.	[54, 150]
NX and doxorubicin-induced rats	CRS	TGF-β1/Smad	Upregulating protein expression of TGF-β1 and p-Smad3.	[53, 59]
NX -and doxorubicin-induced rats	CRS	TGF-β1/Smad and BMP/Smad	Upregulating protein expression of TGF-β and Smad3 and downregulating protein expression of Smad1 and Smad5.	[49, 50]
Mini-pig with left ventricular ischaemia and CKD	CRS	TGF-β1/Smad	Upregulating protein expression of TGF-β and p-Smad3.	[60]
NX and MI-induced rats	CRS	TGF-β1/Smad	Upregulating intrarenal p-Smad2 protein expression.	[61]
MI-induced rats	CRS	TGF-β1/Smad	Upregulating TGF-β and p-Smad2 protein expression.	[62]
TAC-induced mice and HKC-8 cells treated by serum from TAC mice	CRS2	Wnt/β-catenin	Upregulating protein expression of Wnt ligands, active β-catenin and hyperactivate RAS components.	[7]
NX rats	CRS4	Wnt/β-catenin	Upregulating protein expression of Wnt ligands and activating β-catenin.	[65]
Renal IRI-induced mice	CRS3	Wnt/β-catenin	Upregulating p-β-catenin protein expression and downregulating β-catenin nuclear translocation.	[66]
NX and doxorubicin-induced rats	CRS	Wnt/β-catenin	Upregulating protein expression of Wnt1, Wnt4 and β-catenin.	[50]
hHcys-induced mice	CRS	Wnt/β-catenin	Upregulating mRNA and protein expression of Wnt1 and upregulating protein expression of β-catenin and p-GSK-3β.	[68]
Patients	CRS2	RAAS	A high urinary podocin/creatinine ratio.	[71]

exhibited increased levels of phosphorylated apoptosis signal-regulated kinase 1 and NF-κB in the tissues of CRS rats and neonatal rat cardiac fibroblasts/myocytes [38]. Chronic inflammation is involved in chronic renal remodelling in patients with heart failure. Animal models with CRS2 presented increased numbers of $CD3^+$ and $CD68^+$ immune cells along with severe interstitial fibrosis in renal tissues [39]. In addition, altered glutathione levels were observed in transgenic mice with dilated cardiomyopathy [40]. Overall, the hyperactive NF-κB signalling pathway is involved in the progression of CRS2.

Oxidative stress and inflammation in CRS3. CRS3 is characterised by AKI as a precursor to subsequent CVD [41]. Oxidative stress has been shown to be involved in the pathophysiology of CRS3. Mice with CRS3 induced by unilateral renal ischaemia/reperfusion injury (IRI) presented a reduced left kidney weight and impaired renal function, along with increased intrarenal iNOS protein expression [42]. Additionally, Caio-Silva et al. reported increases in superoxide dismutase (SOD) activity and the activities of nicotinamide adenine dinucleotide phosphate oxidase (NOX) and nitric oxide synthase in the hearts of mice with unilateral renal IRI-induced cardiac remodelling [43]. In summary, the hyperactive NF-κB signalling pathway has been implicated in CRS3.

Oxidative stress and inflammation in CRS4. CRS4, which is associated with high morbidity and mortality rates, has become a clinical problem worldwide. The latest publication revealed changes in the levels of inflammatory mediators such as TNF-α, IL-6 and high-sensitivity C-reactive protein (hs-CRP) in 129 adults, suggesting that these inflammatory factors are associated with lifestyle-related cardiorenal risk [44]. In addition, peroxisome proliferator-activated receptor alpha (PPARα) protein expression was significantly downregulated in the left ventricle of NX rats [45]. Thus, oxidative stress and inflammation are implicated in CRS4.

Oxidative stress and inflammation in CRS5. To date, few publications have documented the activation of oxidative stress and inflammation in CRS5. Liu et al. reported increases in the levels of IL-1, IL-6 and TNF-α and a decrease in the IL-10 levels in the serum and heart but an increase in the heart levels of ROS, SOD, glutathione peroxidase and MDA in mice with lipopolysaccharide-induced CRS5 [46].

Oxidative stress and inflammation in uncategorised CRS. The above studies reported CRS according to the five-type classification. Oxidative stress and inflammation in CRS patients described in some publications did not reveal a specific subtype. Clinical observations revealed that the levels of pentraxin 3, hs-CRP and TNF-α were higher in CKD patients with CVD than in those without CVD [47]. A recent study revealed that renal function decreases, albuminuria and the urine albumin-to-creatinine ratio increase, NF-κB, NOX2 and NOX4 are upregulated, and the Nrf2 downstream target gene products MnSOD and catalase are downregulated in the kidney tissues of high-salt diet-induced Dahl salt-sensitive rats with nondiabetic cardiorenal disease [48]. Chua et al. showed that rats with CRS induced by NX and doxorubicin exhibit a low left ventricular ejection fraction and larger left ventricular chamber size. The left ventricular myocardium of rats with CRS exhibited increased expression of inflammation-associated proteins, including TNF-α, NF-κB, matrix metalloproteinase (MMP)-2, MMP-9, and IL-1β, and oxidative stress-associated proteins, such as NOX1, NOX2, NOX4 and their oxidised proteins [49]. Additionally, doxorubicin/p-cresol-treated H9c2 cells presented increased expression of proteins associated with oxidative stress, including NOX1, NOX2 and their oxidised proteins [49]. The same research group further showed that rats with CRS induced by NX and doxorubicin displayed impaired renal function. The kidney tissues of rats with CRS presented increased expression of

Table 2. continued

Patients/animals/cells	Subtype	Pathways	Molecular mechanism and targets	Ref
Patients	CRS1	RAAS	\	[74]
Dahl salt-sensitive rats	CRS	RAAS	Upregulating protein expression of ACE and AT_1R while downregulating protein expression of AT_2R and MAS1 receptor.	[48]
Adenine-induced CKD mice	CRS	Gut microbiota	Increasing abundance of Clostridiales, Dehalobacteriaceae, *Dehalobacterium* and *Corynebacterium*. Increasing plasma TMAO levels. Upregulating mRNA expression of *TGF-β*, *TNF-α* and *CD68*.	[90]
NX and MI-induced rats	CRS2	Gut microbiota	Increasing plasma TMAO levels.	[98]
Trimethylamine-treated rats	CRS	Gut microbiota	Increasing serum levels and urine excretion of TMAO.	[99]
Patient with CRS2	CRS2	miRNAs	Upregulating expression of miR-34a and miR-129-5p.	[105]
DOCA-salt-induced rats with hypertension	CRS	miRNAs	Downregulating expression of miR-200a-3p, miR-200b-3p, miR-200c-3p, miR-141 and miR-429.	[54]
Insulin-resistant and hyperinsulinemic rats	CRS	miRNAs	Changing expression of rno-let-7c, rno-mir-23a, rno-mir-26a and mir-200c.	[106]
Patients	CRS2	miRNA-21	Increasing serum levels of miRNA-21 and cystatin C.	[108]
NX-induced rats	CRS4	miRNA-21	Increasing miR-21-5p expression.	[45]
NX-induced rats	CRS4	lncRNAs	Hyperexpression of lncRNA ANRIL.	[111]

DOCA deoxycorticosterone acetate, *HRGEC* human renal glomerular endothelial cells, *ISCS* Indoxyl sulfate and *p*-cresol sulfate, *LACAL* left-anterior-descending-coronary-artery-ligation, *p-ASK1* phosphorylated apoptosis signal-regulated kinase 1.

inflammation-associated proteins, including TNF-α, NF-κB, MMP-9, and iNOS, and the expression of these proteins was regulated upon activation, and normal T cells expressed and presumably secreted oxidative stress-associated proteins, such as NOX1, NOX2, NOX4 and their oxidised proteins [50]. In addition, increased iNOS expression was observed in rats with MI [51]. Moreover, Savira et al. observed that the protein expression of apoptosis signal-regulating kinase 1, mitogen-activated protein kinases and NF-κB was increased by indoxyl sulfate and *p*-cresol sulfate [52]. In addition, Yang et al. reported that NX and infraperitoneal doxorubicin administration upregulated NOX4, $p22^{phox}$, $p47^{phox}$ and $gp91^{phox}$ protein expression in rats with CRS [53]. Furthermore, increased MCP-1 expression was observed in animal models of CRS [54].

Accumulating evidence indicates that the impairment of Nrf2 is involved in CRS [55]. Liu et al. observed a decrease in the mRNA expression of *Nrf2* and *GCLC* in both rats and Ang II-treated cardiac fibroblasts. Furthermore, rats with CRS presented increased cardiac mRNA expression of *IL-1β*, *IL-6* and *interferon-γ*, as well as increased MDA levels but decreased SOD and glutathione levels [56]. In summary, hyperactive NF-κB and impaired Nrf2 signalling pathways are implicated in CRS.

TGF-β1/Smad signalling pathway in CRS

The TGF-β1/Smad signalling pathway has been identified as a central mediator of multiorgan fibrosis [57, 58] (Fig. 1). Specifically, it is a central contributor to the onset and development of the pathogenesis of CRS. Smad3 activation has been investigated in several publications. Yang et al. reported increased levels of the TGF-β and phosphorylated Smad3 proteins in the left ventricular myocardium and kidney tissues of rats with CRS induced by doxorubicin and NX fed a high-protein diet [53, 59]. Previous publications have shown increased TGF-β protein expression while downregulating Smad1/5 expression in the left ventricular myocardium and TGF-β and Smad3 protein expression was upregulated in the kidney tissues of rats with CRS induced by NX and doxorubicin [49, 50]. In addition, Sheu et al. established a CRS mini-pig model with left ventricular ischaemia mediated by applying an ameroid constrictor over the mid-left-anterior reducing artery and CKD surgery via right nephrectomy with left renal arteriole partial ligation. Elevated TGF-β and Smad3 protein expression levels were observed in the left ventricular myocardium of the model [60].

Smad2 overexpression has also been reported in individuals with CRS. Savira et al. reported that MI rats treated with NX exhibited absolute changes in left ventricular fractional shortening and posterior wall thickness. These changes were accompanied by an increased myocyte cross-sectional area; cardiac and renal interstitial fibrosis; the increased expression of the collagen I, collagen III and tissue inhibitor of metalloproteinase 2 proteins in heart tissues, as well as the upregulation of collagen I, collagen IV, KIM-1 and phosphorylated Smad2 in kidney tissues [61]. Lekawanvijit et al. reported increased levels of the TGF-β and phosphorylated Smad2 proteins in the kidney tissues of MI rats [62]. Zhang et al. suggested that TGF-β increased the expression of cathepsin S and cathepsin K but decreased the expression of cathepsin B and cathepsin L. However, a deficiency of cathepsin S and cathepsin K decreased Smad2/3 activation and extracellular matrix production [58]. Taken together, these findings suggest that the targeted inhibition of the TGF-β1/Smad signalling pathway is a potential therapeutic approach for CRS treatment.

Wnt/β-catenin signalling pathway in CRS

The Wnt/β-catenin pathway is a conserved developmental signalling pathway that critically affects the modulation of tissue development and homoeostasis [63]. Once activated by Wnt, β-catenin is stabilised and enters the nucleus, where it binds to the T-cell factor/lymphoid enhancer-binding factor family of transcription factors and then forms a complex by recruiting the transcriptional coactivator cyclic adenosine monophosphate response element-binding protein-binding protein to transactivate its target genes, such as Twist, Snail1 and matrix metalloproteinases 7 [64] (Fig. 2).

Zhao et al. reported that mice with transverse aortic constriction (TAC) exhibited cardiac hypertrophy, increased inflammation, severe fibrosis and impaired cardiac function [7]. These effects are accompanied by the upregulation of Wnt ligands, the activation of β-catenin and a hyperactive renin–angiotensin system (RAS). In vitro experiments showed that Wnt3a mediated the activation of the RAS in primary cardiomyocytes and cardiac fibroblasts. TAC leads to proteinuria and renal fibrosis, accompanied by the intrarenal downregulation of klotho and activation of β-catenin [7]. Treatment with ICG-001 or losartan attenuated the cardiac impairment, improved heart function, and blunted kidney damage. HKC-8 cells treated with serum from TAC mice presented β-catenin activation and tubular cell injury. Furthermore, an in vitro study suggested that TNF-α inhibited klotho, evoked β-catenin activation, and led to tubular cell lesions [7]. In addition, the same research group showed that cardiac hypertrophy and renal injury were accompanied by the activation of Wnt/β-catenin in NX rats [65]. However, treatment with ICG-001 inhibited the NX-induced intrarenal expression of the fibronectin and podocalyxin proteins, as well as the hypertrophic biomarkers myosin heavy chain β and α-actin, and ameliorated cardiac hypertrophy [65].

Cai et al. demonstrated that, in mice with CRS3, the mitochondrial membrane potential was unstable, mitochondrial ROS production was increased, mitochondrial respiratory complex activity was decreased, and the oxygen consumption rate in mouse cardiomyocytes was reduced [66]. Further results revealed aberrant mitochondrial morphology, dynamics and permeability transition pore opening rates in mouse cardiomyocytes [66]. In mice, cardiomyocyte-specific ablation of FUN14 domain-containing 1 (FUNDC1) led to disorders of mitochondrial homoeostasis and myocardial performance [66]. Furthermore, mice with CRS3 presented increased levels of phosphorylated β-catenin and decreased β-catenin nuclear translocation, thus decreasing FUNDC1-induced mitophagy [66]. In addition, Chen et al. observed that rats with CRS induced by NX and doxorubicin exhibited impaired renal function, and the protein expression of Wnt1, Wnt4 and β-catenin was upregulated in the kidney tissues of rats with CRS [50].

Hyperhomocysteinaemia (hHcys) is a key risk factor for CVD and end-stage renal disease. Progranulin, an autocrine growth factor, is present in a myriad of organs and plays a critical role in a wide range of pathophysiological processes, such as tissue development, inflammation modulation, the host defence response and insulin resistance [67]. Fu et al. reported that the kidneys of mice with hHcys presented upregulated mRNA expression of *Wnt1*, *Wnt2b*, *Wnt3*, *Wnt3a* and *Wnt4* [68]. Furthermore, intrarenal *Wnt1* mRNA and protein expression was significantly upregulated in hHcys mice, which was further enhanced by impaired progranulin. This study also revealed that the upregulation of Wnt1 protein expression was mainly observed in glomeruli [68]. Additionally, dephosphorylated β-catenin induced increases in total plasma homocysteine levels and β-catenin expression. Moreover, the results revealed that the upregulation of β-catenin protein expression was related to the upregulation of phosphorylated glycogen synthase kinase 3 beta (GSK-3β) protein expression. Progranulin deficiency enhanced the effect of homocysteine on the intrarenal levels of phosphorylated GSK-3β and β-catenin [68]. In contrast, treatment with recombinant human progranulin suppressed the intrarenal homocysteine-induced Wnt/β-catenin signalling pathway in hHcys mice. Similar results were observed in *L*-homocysteine-induced podocytes. In addition to recombinant progranulin, Dkk1 restored the protein expression of nephrin and podocin in podocytes after homocysteine treatment [68]. Therefore, the Wnt/β-catenin signalling pathway is an essential pathogenic mediator of CRS.

The RAAS in CRS

RAAS components, including angiotensinogen (AGT), renin, angiotensin (AngI), angiotensin-converting enzyme (ACE), ACE2, Ang II, angiotensin (1–7) (Ang1-7), angiotensin II type 1 receptor (AT_1R), angiotensin II type 2 receptor (AT_2R), Mas receptor (MasR) and mineralocorticoid receptor, are crucial for preserving arterial blood pressure and the sodium–water balance [69] (Fig. 2). The RAS plays a critical role in cardiovascular control and the pathogenesis of cardiovascular diseases [70]. The underlying mechanisms of CRS include venous congestion and arterial underfilling. Arterial underfilling results in a hyperactive RAAS and provokes sodium reabsorption and vasoconstriction. Venous congestion induces and perpetuates these aberrant changes. An earlier clinical study revealed that the urinary podocin/creatinine ratio was high in patients with CRS2 compared with controls [71]. A recent study showed decreased ACE2 levels in coronavirus disease 2019 patients; animal models of AKI, heart failure and diabetes; and severe acute respiratory syndrome coronavirus 2-infected cardiomyocytes, which were associated with decreased levels of IL-10, SOD2 and catalase and upregulated mRNA expression of *IL-1β*, *IL-6*, *IL-17* and *TNF-α* [72]. Genetic ACE2 deletion resulted in the upregulation of IL-1β, IL-6, IL-17 and TNF-α. Inflammatory cytokine IL-17 signalling results in both protective and harmful immune responses. A study of the underlying mechanism indicated that IL-17A directly activates myofibroblasts and fibrotic niche formation in Group 3 innate lymphoid cells [73]. Previous publications reported that CRS1 development and a lack of angiotensin-converting enzyme inhibitor (ACEI) and angiotensin II receptor blocker (ARB) use were the two most essential independent predictors of in-hospital mortality. Further study revealed that the associations between a lack of ACEI and ARB use and elevated mortality remained significant in patients who did not develop CRS1 [74]. The latest results revealed the upregulation of the ACE and AT_1R proteins and downregulation of AT_2R and MAS1 receptors in the kidney tissues of high-salt diet-induced Dahl salt-sensitive rats with nondiabetic cardiorenal disease [48]. As mentioned above, the RAAS plays an essential role in the onset and development of CRS.

Circulating fibroblast growth factor 23 (FGF23) levels in individuals with CRS

Many publications have shown that an increasing risk of CKD-related death is closely associated with cardiovascular complications, particularly left ventricular hypertrophy (LVH) [75, 76]. FGF23, a circulating phosphate-modulating protein hormone secreted by bone cells, suppresses the synthesis of active vitamin D and promotes phosphate excretion by the kidney [77, 78]. Moreover, it has been shown to have paracrine effects on several cells, such as cardiomyocytes, hepatocytes and immune cells. FGF23 levels are increased early in individuals with CKD and are independently related to LVH, sudden cardiac death, heart failure and death [76, 78, 79]. An earlier study indicated that circulating FGF23 levels are increased in patients with CKD and induce LVH by a fibroblast growth factor receptor (FGFR)-dependent mechanism [80]. Further study revealed that FGF23 could activate FGFR4 expression, which was identified as a receptor for FGF23 on cardiac myocytes, to stimulate phospholipase Cγ/calcineurin/nuclear factor in the activated T-cell signalling pathway [75]. The inhibition of FGFR4 ameliorated FGF23-mediated hypertrophy of cardiac myocytes and alleviated LVH in CKD rats [75]. However, in mice lacking FGFR4 expression, LVH cannot be induced in response to increased FGF23 levels, whereas in mice with FGFR4 knockdown, LVH can occur [75]. Verhulst et al. documented increased serum FGF23 levels in rats with CRS4 [81]. A recent study suggested that excessive FGF23 levels induced renal fibrosis by the activation of the FGFR4/β-catenin signalling pathway in CRS2

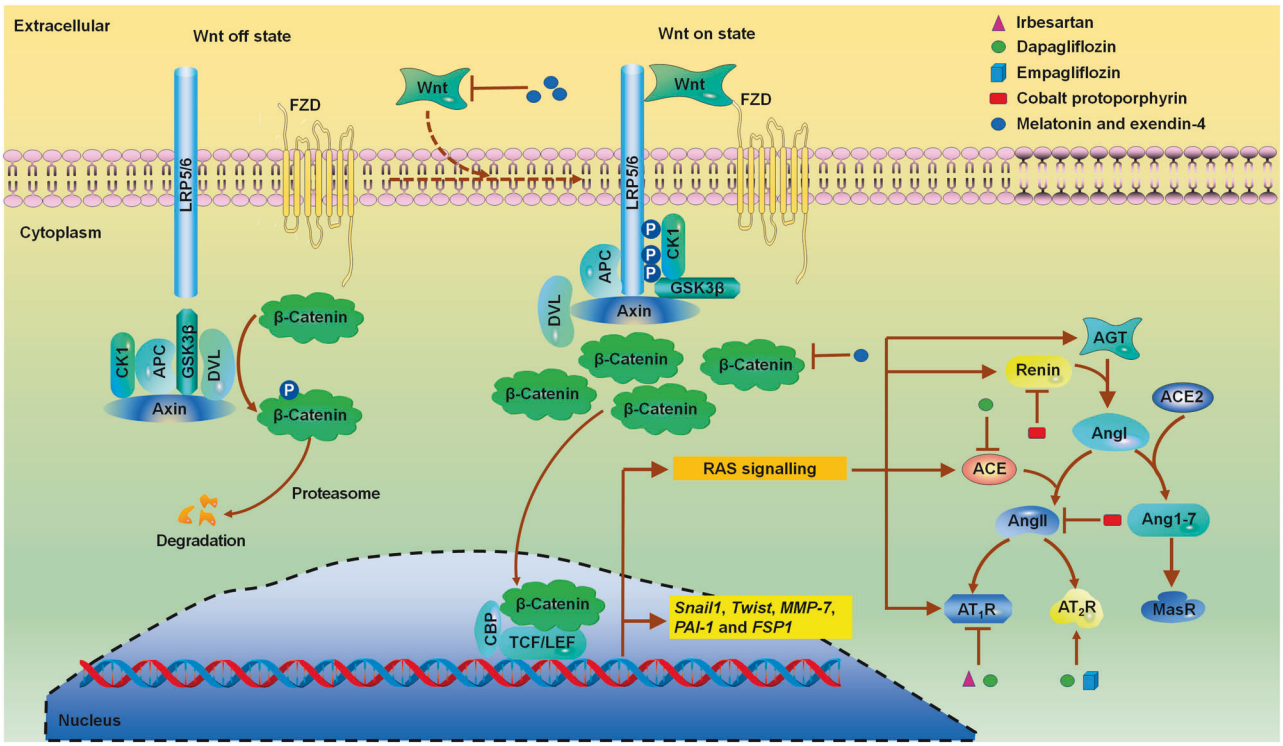

Fig. 2 The activation of the Wnt/β-catenin pathway and its downstream RAS signalling are critical therapeutic targets in CRS. RAS signalling is a downstream target of the Wnt/β-catenin pathway. Activation of the Wnt/β-catenin and RAS signalling pathways is implicated in the progression of CRS, causing damage. Treatment with melatonin and exendin-4 improves cardiorenal function and abolishes cardiac and renal fibrosis by downregulating the expression of the Wnt and β-catenin proteins. Similarly, irbesartan blocks the interaction of AngII and AT_1R, and cobalt protoporphyrin ameliorates RAS dysfunction by decreasing the levels of AngII and renin. Overall, the inhibition of the Wnt/β-catenin pathway and its downstream target RAS signalling pathway exerts antifibrotic effects on CRS.

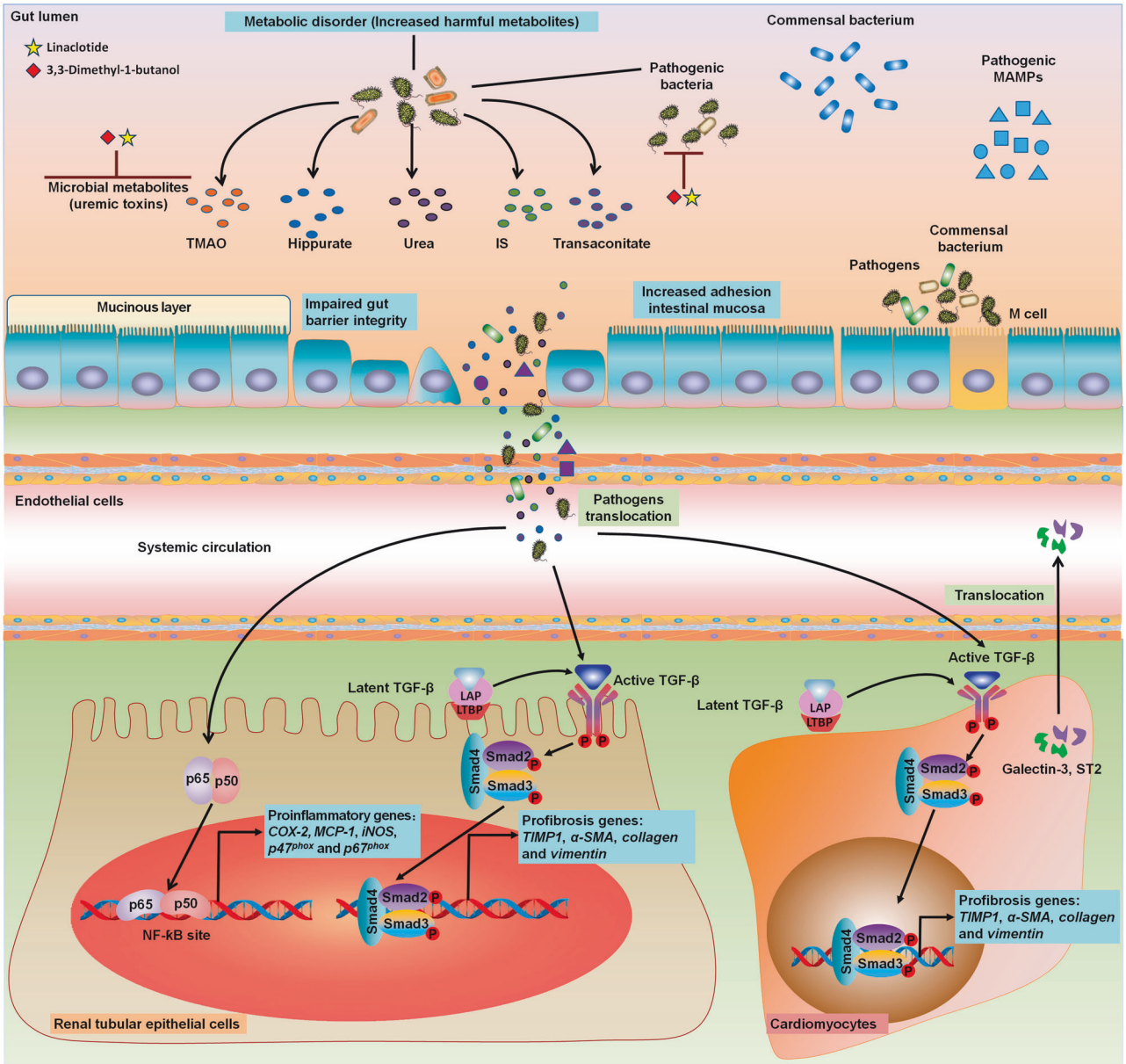

Fig. 3 The reshaping of the gut microbiota is a potentially novel therapy for the treatment of CRS. An aberrant gut–cardiorenal axis plays an important role in the pathogenesis of CRS. CRS leads to microbial dysbiosis, while pathogenic bacteria and their metabolites, such as uraemic toxins, including TMAO, indoxyl sulfate, hippurate, creatinine, urea and *trans*-aconitate, work as multikingdom intermediates for proinflammatory and profibrotic gene expression via the IκB/NF-κB and TGF-β/Smad signalling pathways, forming a vicious cycle. Treatment with linaclotide regulates bacterial abundance and reduces plasma levels of uraemic toxins, exerting cardioprotective and renoprotective effects on individuals with CRS.

rats [82]. These findings suggest that FGF23 enhances LVH by the activation of FGFR4 expression. Therefore, FGFR4 could be considered a therapeutic target for decreasing the CVD risk in CKD patients.

Microbial dysbiosis in CRS

The human gut harbours a microbial ecosystem that plays essential roles in maintaining intestinal barrier integrity, regulating metabolic function and modulating host immunity in health and disease [83] (Fig. 3). An emerging multiomic approach has been applied to elucidate novel and potentially key mechanisms involved in CRS [84]. An increasing number of publications have shown that dysbiosis of the gut microbiota is a complication of a variety of diseases, such as cancer, CVD and CKD [73, 85–87]. Increasing evidence has suggested that microbial dysbiosis is associated with CRS [88, 89]. Nanto-Hara et al. reported crosstalk between the gut microbiota and CRS. A 16S rRNA analysis revealed that the richness of the gut microbiota was significantly decreased in adenine-treated mice compared with control mice [90]. This effect was accompanied by reduced α diversity in adenine-induced adenine-treated mice. A weighted UniFrac analysis revealed that the gut microbial composition differed between control and adenine-treated mice [90]. A subsequent microbial population analysis indicated that the relative abundances of Clostridiales and Dehalobacteriaceae were increased in adenine-treated mice [90]. Finally, at the genus level, the relative abundance of *Dehalobacterium* was significantly increased in adenine-treated mice, which was accompanied by a significant increase in the relative abundance of *Corynebacterium* among minor populations [90].

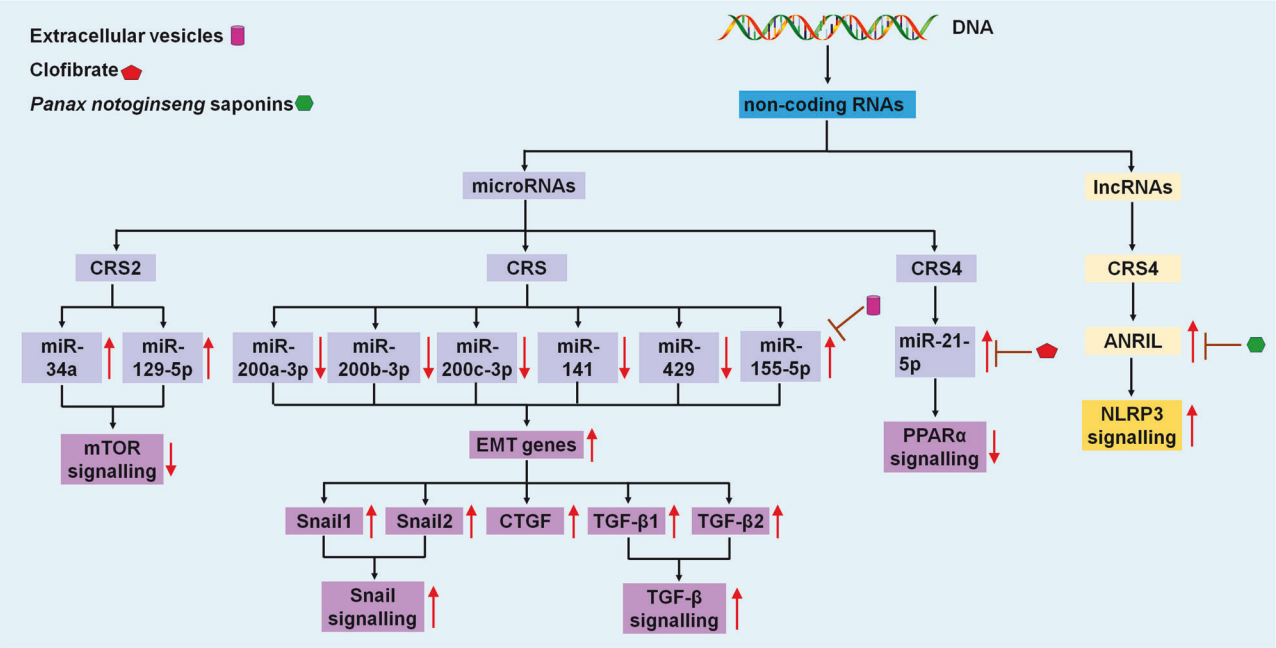

Fig. 4 The dysregulation of noncoding RNAs is an alternative therapeutic target in CRS. The upregulated expression of microRNAs and lncRNAs, which are associated with the activation of mTOR, Snail, TGF-β, PPARα and NLRP3 signalling, has been observed in individuals with CRS. Treatment with extracellular vesicles, clofibrate and *Panax notoginseng* saponins ameliorates CRS by regulating mTOR, Snail, TGF-β, PPARα and NLRP3 signalling via the inhibition of the expression of microRNAs and lncRNAs.

Several seminal publications have highlighted that microbial metabolites work as multikingdom intermediates for the crosstalk of multiple organs [83, 91] (Fig. 3). Due to rapid advances, metabolomics has been used as an important tool for identifying disease biomarkers and understanding the biochemical mechanism of CRS [92]. An increasing number of studies have documented the accumulation of a variety of circulating uraemic toxins, such as TMAO, indoxyl sulfate, phenyl sulfate, hippurate, creatinine, urea, *trans*-aconitate and spermine, which are critical mediators of aberrant communication between the heart, kidneys and other organs that exacerbates CVD and CKD [93–97] (Fig. 3). Using a metabolomic technique, Nanto-Hara et al. observed significant increases in the plasma levels of TMAO, indoxyl sulfate, hippurate, creatinine, urea and *trans*-aconitate in mice with adenine-induced CKD [90] (Fig. 3). TMAO, a product of carnitine and choline metabolism by the gut microbiota, also known as a gut-derived uraemic toxin, plays an essential role in the aberrant gut–cardiorenal axis. The same research group further suggested increases in plasma TMAO and galectin-3 levels but no significant changes in the plasma levels of indoxyl sulfate, phenyl sulfate, ST2, and growth differentiation factor 15. These changes were accompanied by increased mRNA expression of *TGF-β*, *TNF-α* and *CD68*, which led to increased renal inflammation and fibrosis and cardiac fibrosis in choline-fed atherosclerotic mice [90]. Similarly, elevated plasma levels of TMAO are observed in NX- and MI-induced rats with CRS2 [98]. TMAO is produced from the oxidation of trimethylamine to flavin monooxygenases. Maksymiuk et al. reported that an increase in serum levels and urine excretion of TMAO was accompanied by mild degeneration of renal bodies with glomerulosclerosis, but RAS expression was not significantly altered in trimethylamine-treated rats [99]. Collectively, the effects of the gut microbiota and its metabolites on the gut–cardiorenal axis provide relatively novel clues for the study of the pathological mechanism of CRS.

The dysregulation of noncoding RNAs in CRS

RNA polymerase II-mediated mammalian genome transcription mainly involves protein-coding mRNAs and noncoding RNA transcriptional units. Furthermore, noncoding RNAs, which include mainly microRNAs (miRs) and long noncoding RNAs (lncRNAs), refer to transcripts that are unable to be translated into proteins [100, 101]. miRNAs, small noncoding RNAs that modulate gene expression, work as essential genetic regulators to instruct cellular pathways by communicating with a wide range of downstream target genes, causing miRNA-induced gene silencing [102–104]. The latest bioinformatics analysis revealed increased expression of miR-34a in CRS patients compared with CHF patients and increased expression of miR-129-5p in CHF patients and patients with CRS, which was associated with decreased mammalian target of rapamycin (mTOR) expression [105] (Fig. 4). Moreover, Rafael Soares et al. observed downregulated expression of miR-200a-3p, miR-200b-3p, miR-200c-3p, miR-141 and miR-429, which might be associated with the significant upregulation of epithelial–mesenchymal transition-related genes such as *TGF-β1*, *TGF-β2*, *connective tissue growth factor*, *Snail1* and *Snail2* in deoxycorticosterone-acetate-salt-induced CRS rats with hypertension [54]. These findings suggest that the miR-200-TGF-β axis is one of the key pathways involved in CRS [54] (Fig. 4). Early publications revealed the overexpression of p70 S6 kinase 1 (S6K1)-modulating miRNAs such as rno-let-7c, rno-mir-23a and rno-mir-26a and the moderate regulation of mir-200c expression in insulin-resistant and hyperinsulinaemic obese Zucker rats with CRS [106]. A recent in silico integrative approach revealed that 24 key miRNAs, such as hsa-mir-122-5p, hsa-mir-29b-3 and hsa-mir-21-5p, are strongly correlated with the pathological mechanism of CRS [107].

Among all miRNAs, miRNA-21 has been extensively studied as a therapeutic target for CRS. A previous study suggested that the estimated glomerular filtration rate and serum levels of cystatin C and heart-type fatty acid-binding protein correlated with *miR-21* expression in patients with CRS2 and CHF [108]. Further analysis demonstrated that serum miR-21 levels, increased serum levels of cystatin C and KIM-1, hyperlipidaemia and the ejection fraction were independent risk factors for CRS2 [108]. Furthermore, combining miR-21 with cystatin C showed a high sensitivity and specificity compared with only miR-21 [108]. These findings

indicate that the serum miR-21 level has a moderate diagnostic value for CRS2. However, combining miR-21 expression with cystatin C levels results in a good clinical diagnosis of elderly patients with CRS2. PPARα, a miR-21-5p target, is the primary intracardiac PPAR isoform and is implicated in modulating fatty acid metabolism [45]. Chuppa et al. observed that inhibiting miR-21-5p expression protected against left ventricle hypertrophy and enhanced left ventricle function in NX rats [45] (Fig. 4). Furthermore, mRNA sequencing revealed that inhibiting miR-21-5p expression altered the expression of genes in the PPARα-regulated pathway in the left ventricle of NX rats [45]. Clofibrate, a PPARα agonist, improved cardiac function and attenuated left ventricle dilation in NX rats [45]. This study revealed that PPARα is regulated by miR-21-5p and that activated PPARα ameliorates renal and cardiac dysfunction in individuals with CRS4 (Fig. 4). Collectively, these findings suggest that miR-21 is a potential therapeutic target for CRS4.

LncRNAs, noncoding RNAs that are longer than 200 nucleotides, modulate a variety of gene functions and cellular pathways, although they often have low stability and abundance [109]. Early publications identified a potential role for lncRNAs in venous congestion by constructing and observing an lncRNA–mRNA coexpression network [110]. A recent study showed that overexpression of antisense noncoding RNA in the INK4 locus (ANRIL) led to the exacerbation of nucleotide-binding domain, leucine-rich-containing family pyrin domain-containing-3 (NLRP3) inflammasome-mediated cardiomyocyte pyroptosis [111] (Fig. 4). Overall, the dysregulation of noncoding RNAs is implicated in the pathological mechanism of CRS.

TREATMENT OF CRS

Traditional therapeutic strategies for CRS mainly target haemodynamic and neurohormonal pathways. Based on the underlying molecular mechanisms, CRS treatments have different therapeutic effects on various pathogeneses. This review highlights the therapeutic effects of chemical drugs, natural products, complementary therapies, blockers and agonists in the treatment of CRS, categorised by their ability to regulate the activation of various molecular pathways (Table 3).

Treatment of CRS by inhibiting oxidative stress and inflammation

Among the complex pathogenic mechanisms of CRS, oxidative stress and inflammation have been observed in individuals with different subtypes of CRS. Therefore, treatment strategies that target oxidative stress and inflammation are used for the treatment of different types of CRS. Various treatments that target IκB/NF-κB or Keap1/Nrf2 and their downstream genes have been explored.

Treatment of CRS1. The IκB/NF-κB signalling pathway is extensively considered a therapeutic target in various diseases (Fig. 1). A recent study demonstrated that histone lactylation caused by the enrichment of 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3-mediated tubular glycolytic reprogramming was increased in the promoters of NF-κB target genes, such as RelA, RelB and inhibitor of NF-κB kinase subunit beta [29]. Further study revealed that the specific deletion of 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 suppressed the activation of IκB kinase beta, IκBα and p65 [29]. Treatment with apela significantly decreased the plasma levels of N-terminal pro-brain natriuretic peptide, creatinine and urea but increased the left ventricular ejection fraction in CRS mice. These changes were accompanied by decreased levels of MCP-1 and TNF-α in the plasma and kidney [36]. Similar results were also observed in glomerular endothelial cells exposed to Ang II. Furthermore, phosphorylated NF-κB was downregulated after apela treatment in both MI-induced mice and glomerular endothelial cells exposed to Ang II [36]. However, an inhibitor of the apelin peptide jejunum receptor partially abolished the beneficial effect of apela [36]. Thus, these findings indicate that apela ameliorates cardiorenal pathology in CRS1 mice.

HO-1 is a novel therapeutic target to prevent CVD, renal dysfunction and the onset of CRS [112]. An earlier publication showed that treatment with cobalt protoporphyrin, an HO-1 inducer, ameliorated renal vasoconstriction and damage in MI mice induced by C57 and, more evidently, in severe combined immunodeficiency mice [113]. In addition, cobalt protoporphyrin reduced plasma creatinine levels in MI model mice. However, stannous mesoporphyrin partially abolished this beneficial effect [113]. This study demonstrated that an HO-1 inducer attenuated type 1 CRS.

Isoproterenol is often used as an AHF model because it transiently induces hypotension, extreme tachycardia and myocyte apoptosis. Johnson et al. reported that treatment with the iron chelator desferrioxamine downregulated the mRNA expression of *NGAL*, *HO-1*, *IL-6* and *MCP-1* while increasing glutathione levels and decreasing MDA levels in the kidney tissues of isoproterenol-induced model mice [37]. Additional results revealed substantial Fe-dependent cell damage, and Fe independently increased the mRNA expression of *HO-1* and *IL-6* in isoproterenol-treated HK-2 cells [37]. Overall, CRS1 can be ameliorated by regulating the IκB/NF-κB and Keap1/Nrf2 signalling pathways.

Treatment of CRS2. An increasing number of publications have used a wide range of natural products to treat various diseases, including heart disease, renal disease and CRS [38, 114–118]. A previous publication suggested that higenamine, a natural product from *Aconitum*, improves cardiac function in individuals with heart failure [119]. Higenamine treatment reduces the serum levels of creatinine, urea and brain natriuretic peptide and enhances left ventricular remodelling and systolic function in CRS rats [38]. A mechanistic study revealed that higenamine downregulated NF-κB protein expression in the cardiorenal tissues of CRS2 rats and in neonatal rat cardiac fibroblasts and cardiomyocytes [38] (Fig. 1). An earlier study showed that liposomal clodronate inhibited tubular cell apoptosis, ED-1^{+} macrophage infiltration and interstitial fibrosis in MI rats with CRS2 [35]. N-acetylcysteine, an antioxidant, serves as a precursor for the formation of glutathione in CKD. N-acetylcysteine had a slight effect on the expression of intrarenal *IL-1α* and *TNF-α* mRNAs in mice with dilated cardiomyopathy. These changes were accompanied by increased expression of IL-10 at both the mRNA and protein levels [40]. Therefore, these findings indicate that oxidative stress and inflammation might be considered therapeutic targets in patients with CRS2.

Treatment of CRS3. Early studies suggested that the potential cause of myocardial injury in CRS3 patients was associated with mitochondrial dysfunction, which was accompanied by oxidative stress and inflammation [42, 120]. Vitamin C, which is known as an antioxidant, has protective effects on the kidneys, heart and vascular endothelial cells. A recent study showed that vitamin C treatment preserved the left kidney weight, improved renal function, decreased nitric oxide levels, downregulated iNOS expression and upregulated the expression of constitutive NOS isoforms [42]. Moreover, Wang et al. observed that the overexpression of Bcl-2-associated X (Bax) inhibitor-1 decreased the expression of MCP-1 and IL-6, which manifested as relieved myocardial inflammation in Bax inhibitor-1 transgenic mice with MI and CRS3 [120]. Taken together, these findings indicate that oxidative stress and inflammation play indispensable roles in preventing and treating CRS3.

Treatment of CRS4. Natural products have been widely used to treat a wide range of diseases in long-term clinical practice [121–123]. Increasing evidence has shown that natural products

Table 3. The potential therapies of CRS by chemical drugs, natural products and complementary agents.

Treatment	Model	Subtype	Mechanism	Targets	Refs
Apela	MI-induced mice	Type 1 CRS	IκB/NF-κB	Downregulating protein expression of TNF-α, MCP-1 and p-NF-κB.	[36]
Iron chelator desferrioxamine	Isoproterenol-induced mice and HK-2 cells	CRS1	Inflammation	Downregulating mRNA expression of *NGAL*, *HO-1*, *IL-6* and *MCP-1*. Increasing glutathione levels while decreasing MDA levels.	[37]
Higenamine	LACAL and NX-induced rats and myocyte cells	CRS2	IκB/NF-κB	Downregulating NF-κB protein expression.	[38]
Liposome clodronate	MI-induced rats	CRS2	Inflammation	Inhibiting ED-1^{+} macrophage infiltration.	[35]
N-acetylcysteine	Dilated cardiomyopathy mice	CRS2	Inflammation	Downregulating mRNA expression of *IL-1α* and *TNF-α* while upregulating mRNA and protein expression of IL-10.	[40]
Vitamin C	Unilateral renal IRI-induced mice	CRS3	IκB/NF-κB	Downregulating protein expression of iNOS and constitutive NOS isoforms and decreasing nitric oxide levels.	[42]
Bax inhibitor-1	MI-induced transgenic mice	CRS3	IκB/NF-κB	Downregulating protein expression of MCP-1 and IL-6.	[120]
Apocynin	NX-induced rats	CRS4	Inflammation	Reducing MDA levels and NOX activity	[125]
Apocynin	Ang II-induced cardiac cells	CRS4	IκB/NF-κB	Decreasing NOX levels.	[125]
Saponin	NX-induced rats	CRS4	Inflammation	Downregulating protein expression of NLRP3 and IL-1β.	[111]
Melatonin and exendin-4	NX and doxorubicin-induced rats	CRS	IκB/NF-κB	Downregulating protein expression of TNF-α, NF-κB, IL-1β, iNOS, CD14, CD68, NOX1, NOX2 and NOX4.	[49, 50]
Melatonin and exendin-4	Doxorubicin/p-cresol-treated H9c2 cells	CRS	Inflammation	Downregulating protein expression of NOX1, NOX2 and their oxidised proteins.	[49]
Dapagliflozin	High-salt-induced rats	CRS	IκB/NF-κB and Keap1/Nrf2	Downregulating protein expression of NF-κB, IL-1β, IL-6, NOX2 and NOX4 while upregulating protein expression of MnSOD and catalase.	[48]
Naringenin	NX and isoproterenol-induced rats	CRS	Keap1/Nrf2	Downregulating protein expression of IL-1β and IL-6 while upregulating Nrf2 protein expression.	[56]
Naringenin	Ang II-treated cardiac fibroblasts	CRS	Keap1/Nrf2	Upregulating Nrf2 protein expression.	[56]
ASK1 inhibitors	ISCS-induced neonatal rat cardiac myocyte and fibroblast	CRS	IκB/NF-κB	Inhibiting p-NF-κB protein expression.	[52]
Hydrogen sulfide	\	CRS	IκB/NF-κB and Keap1/Nrf2	Regulating IκB/NF-κB and keap1/Nrf2 signalling pathways	[55]
Extracorporeal shock wave	LACAL and NX-induced mini-pigs	CRS	Inflammation	Downregulating protein expression of NOX1 and NOX2.	
Ultrafiltration or diuretic therapies	Patients	CRS	Inflammation	No significant changes in plasma levels of SOD, catalase, MDA and glutathione peroxidase.	[132]
Entresto	High-protein-diet-induced rats	CRS	TGF-β1/Smad	Downregulating protein expression of TGF-β and p-Smad3	[53]
Empagliflozin	NX and doxorubicin-induced rats	CRS	TGF-β1/Smad	Downregulating protein expression of TGF-β and Smad3.	[59]
Melatonin and exendin-4	NX and doxorubicin-induced rats	CRS	TGF-β/Smad	Downregulating protein expression of TGF-β and p-Smad3 while upregulating protein expression of p-Smad1 and p-Smad5.	[49, 50]
G226	NX and MI-induced rats	CRS	TGF-β1/Smad	Downregulating p-Smad2 protein expression.	[61]
Extracorporeal shock wave	LACAL and NX-induced mini-pigs	CRS	TGF-β1/Smad	Downregulating protein expression of TGF-β and p-Smad3.	[60]
Melatonin and exendin-4	NX and doxorubicin-induced rats	CRS	Wnt/β-catenin	Downregulating protein expression of Wnt1, Wnt4 and β-catenin.	[50]
Cobalt protoporphyrin	MI-induced mice treated by C57	Type 1 CRS	RAS	Decreasing plasma levels of creatinine, renin and Ang II.	[113]
ACEI or ARB	Patients	CRS2	RAAS	\	[71]
Irbesartan	NX and MI-induced rats	CRS	RAAS	Blocking combination of Ang II and AT_1R.	[139]
Dapagliflozin or empagliflozin	Dahl salt-sensitive rats	CRS	RAAS	Downregulating protein expression of ACE and AT_1R while upregulating AT_2R protein expression.	[48, 59]
25-Hydroxyvitamin D	Black and white subjects	CRS	RAAS	Suppressing RAAS activity.	[142]

Table 3. continued

Treatment	Model	Subtype	Mechanism	Targets	Refs
Linaclotide	Adenine-induced CKD mice	CRS	Gut microbiota	Decreasing abundance of Clostridiales, Dehalobacteriaceae, *Dehalobacterium* and *Corynebacterium*. Decreasing plasma TMAO levels.	[90]
3,3-Dimethyl-1-butanol	NX and MI-induced rats	CRS2	Gut microbiota	Decreasing plasma TMAO levels.	[98]
Modulators for *miR-200*	\	CRS	miRNAs	Regulating mTOR/S6K1 signaling pathway.	[106]
Clofibrate	NX-induced rats	CRS4	miRNAs	Inhibiting miR-21-5p expression.	[45]
Extracellular vesicles	DOCA-salt-induced rats	CRS	miRNAs	Suppressing miR-155-5p expression.	[54]
Saponins	Doxorubicin/p-cresol-treated H9c2 cells	CRS4	lncRNAs	Downregulating expression of lnRNA ANRIL.	[111]

DOCA deoxycorticosterone acetate, *HRGEC* human renal glomerular endothelial cells, *ISCS* Indoxyl sulfate and *p*-cresol sulfate, *LACAL* left-anterior-descending-coronary-artery-ligation.

ameliorate CRS4 by inhibiting oxidative stress and inflammation. Two examples are described below. Apocynin, a naturally occurring acetophenone in the roots of *Picrorhiza kurroa* and *Apocynum cannabinum*, is an inhibitor of nicotinamide adenine dinucleotide phosphate oxidase [124]. Yang et al. reported that treatment with apocynin reduced MDA levels and NOX activity in NX rats with CRS4 [125]. In vitro experiments also suggested that Ang II-treated cardiac cells presented decreased NOX levels [125]. Saponin, extracted from the roots and rhizomes of *Panax notoginseng* (Burk.) F. H. Chen., is widely used to treat CVD [126]. A recent study reported that saponin enhanced cardiac function and ameliorated cardiac fibrosis and pyroptosis in NX-induced mice with CRS4 and hypoxia-injured H9c2 cells [111]. Further mechanistic studies revealed that saponins inhibited the expression of the pyroptosis-related proteins NLRP3 and IL-1β [111]. Collectively, these studies suggest that natural products represent an important therapy for the treatment of CRS4.

Treatment of CRS. The pathogenesis of CRS is very complex. Therefore, several studies have reported the treatment of CRS but not specific types of CRS. Chen et al. showed that treatment with either melatonin or exendin-4 downregulated the protein expression of TNF-α, NF-κB, IL-1β, iNOS, CD14 and CD68, which was accompanied by decreased expression of NOX1, NOX2, NOX4 and oxidised proteins in both the cardiac and renal tissues of CRS rats [49, 50] (Fig. 1). An in vitro study revealed decreased levels of NOX1, NOX2 and oxidised proteins [49]. The same research group further showed that exendin-4 had a better effect than melatonin on cardioprotection and the attenuation of renal deterioration, while combined therapy with melatonin and exendin-4 had a stronger effect than treatment with either agent alone [49, 50]. Recent studies suggested that dapagliflozin and empagliflozin downregulated the protein expression of NF-κB, IL-1β, IL-6, NOX2 and NOX4 but upregulated the protein expression of MnSOD and catalase in rats with high-salt-induced CRS [48, 59] (Fig. 1).

Natural products, along with their structural analogues, have historically made great contributions to pharmacotherapy [127–130]. Increasing evidence suggests that natural products are used for the treatment of heart failure and kidney disease. Naringenin is a trihydroxyflavanone that is present in different citrus fruits, such as pomelos, oranges, and grapefruits, as well as in coffee, tomatoes and fenugreek, and protects against inflammation [131]. Liu et al. reported that naringenin attenuates cardiac remodelling and dysfunction, accompanied by decreased protein expression of IL-1β and IL-6, decreased MDA levels, and increased Nrf2 protein expression in the heart [56].

Several inhibitors repress the hyperactive NF-κB signalling pathway, resulting in the partial abolishment of the protective effect of indoxyl sulfate and *p*-cresol sulfate on cardiorenal cell functions [52]. Hydrogen sulfide, a gaseous signalling molecule, modifies cysteine residues on critical inflammation-associated signalling molecules, including keap1/Nrf2, IκB/NF-κB and hypoxia-inducible factor-1α, thereby protecting against oxidative stress [55]. Moreover, extracorporeal shock wave treatment has been shown to be effective at downregulating the protein expression of NOX1 and NOX2 in minipigs with CRS induced by left-anterior descending-coronary artery constriction and NX [60]. However, Tansu et al. demonstrated that the plasma levels of SOD, catalase, MDA and glutathione peroxidase did not change significantly in patients with CRS after treatment with ultrafiltration or diuretic therapies [132].

Taken together, the abovementioned publications show that signalling pathways related to oxidative stress and inflammation provide rich indicators and multiple options for the treatment of CRS.

Treatment of CRS by targeting the profibrotic TGF-β1/Smad and Wnt/β-catenin signalling pathways

As the TGF-β1/Smad and Wnt/β-catenin signalling pathways are key pathways involved in tissue fibrosis and scarring, studies of

treatments for tissue fibrosis-associated diseases such as cardiac and renal fibrosis have focused on these signalling pathways [133]. Yang et al. documented that kidney injury can be prevented by decreasing the levels of the TGF-β and phosphorylated Smad3 proteins in rats with high-protein-diet-induced CRS [53] (Fig. 1). A recent study revealed that treatment with dapagliflozin downregulated the levels of the TGF-β and Smad3 proteins in high-salt-induced CRS model rats [48] (Fig. 1). Similarly, TGF-β protein expression was also downregulated in rats with CRS induced by NX and doxorubicin after empagliflozin treatment [59] (Fig. 1). Additionally, empagliflozin has a cardioprotective effect by activating β-catenin and promoting its nuclear retention [66] (Fig. 2). Empagliflozin stabilises the mitochondrial membrane potential, inhibits mitochondrial ROS production and increases mitochondrial respiratory complex activity in the cardiomyocytes of CRS3 mice [66]. In addition, empagliflozin normalises the mitochondrial morphology, dynamics and permeability transition pore opening rate in cardiomyocytes. Cardiomyocyte-specific FUNDC1 ablation in mice abrogates the protective effects of empagliflozin on mitochondrial homoeostasis and performance [66]. Empagliflozin activates β-catenin expression and enhances its nuclear retention, thus increasing FUNDC1-mediated mitophagy in the heart; however, a β-catenin inhibitor reverses these effects [66].

Natural compounds have shown beneficial effects for the treatment of cardiac and renal fibrosis [114, 134, 135]. A daphne diterpenoid, daphnepedunin A, from *Wikstroemia chamaedaphne* protects against renal fibrosis and has more beneficial effects than pirfenidone [136]. Further studies of the mechanism revealed that daphnepedunin A inhibits the phosphorylation of protein kinase Cζ/GSK-3β, further increasing the phosphorylation of β-catenin at Ser33/37/Thr41 and ubiquitin-dependent proteolysis to suppress the Wnt/β-catenin signalling pathway [136]. Moreover, combined therapy with melatonin and exendin-4 downregulates the levels of the TGF-β and phosphorylated Smad3 proteins and increases the levels of phosphorylated Smad1 and Smad5, accompanied by decreased levels of the Wnt1, Wnt4 and β-catenin protein, indicating the effective attenuation of renal deterioration in CRS rats [50] (Figs. 1 and 2).

In addition to the chemical drugs mentioned above, natural products can also be used to improve CRS by inhibiting the TGF-β expression. Higenamine treatment reduced TGF-β1 protein expression in CRS rats [38] (Fig. 1). Similarly, ang II-treated cardiac cells presented downregulated TGF-β protein expression after apocynin treatment [125] (Fig. 1). Moreover, a recent study reported that saponins inhibited the mRNA expression of *collagen I*, *collagen III*, *TGF-β* and *alpha-smooth muscle actin*, ameliorating cardiac fibrosis and pyroptosis [111]. Furthermore, the overexpression of the lncRNA ANRIL partially abolished the inhibitory effect of saponins on pyroptosis, whereas Belnacasan, a specific pyroptosis inhibitor, promoted this effect [111].

Additionally, other therapeutic strategies that reduce fibrosis are used to treat CRS. Savira et al. reported that treatment with G226, an apoptosis signal-regulating kinase 1 inhibitor, decreased the levels of phosphorylated Smad2, ameliorating left ventricular dysfunction and renal damage in NX- and MI-induced rats [61]. Moreover, extracorporeal shock wave treatment was shown to be effective at downregulating the protein expression of TGF-β and Smad3 in mini-pigs with CRS [60]. In addition, soluble C-X3-C motif chemokine ligand 1 exacerbated mitochondria-dependent apoptosis by activating the Ras homologue family member A/Rho-associated coiled-coil containing protein kinase 1-Bax pathway and induced fibrosis via the TGF-β/Smad pathway in high glucose-cultured cardiac and renal cells; however, canagliflozin inhibited CX3CL1 expression in high glucose-cultured cardiomyocytes, glomerular mesangial cells, neonatal rat cardiac fibroblasts and renal tubular epithelial cells [137]. In summary, therapeutic approaches to inhibit fibrotic signalling pathways play an irreplaceable role in the treatment of CRS.

Treatment of CRS by targeting the RAAS

Inhibitors of the RAAS, such as renin inhibitors, ACEIs (enalapril, ramipril and benazepril), ARBs (losartan, valsartan and irbesartan) and mineralocorticoid receptor antagonists (MRAs), have advantages in decreasing the hospitalisation and mortality rates of heart failure patients and associated complications [138] (Fig. 2). Le Jemtel et al. suggested that ACEIs or ARBs may prevent urinary podocin loss by reducing the urinary podocin/creatinine ratio, indicating weakened glomerular damage in patients with CRS2 [71]. Moreover, Watanabe et al. reported that irbesartan partially blocked the interaction of Ang II and AT_1R through its strong binding to and slow dissociation from AT_1R, resulting in attenuation of RAAS-induced inflammatory signalling pathways and suppression of cardiac remodelling in NX- and MI-induced CRS rats [139]. The latest clinical study revealed that the lack of use of RAAS blockers leads to a poor prognosis for patients with CRS [140].

Chemical drugs and endogenous component supplements also play important roles in the treatment of CRS by regulating the RAAS. Urbanek et al. reported that dapagliflozin partially abolished the increased protein expression of ACE and AT_1R while increasing AT_2R protein expression, which inhibited RAAS signalling to inhibit proinflammatory mechanisms [48] (Fig. 2). Similarly, treatment with empagliflozin upregulated AT_2R protein expression, resulting in the preservation of the left ventricular ejection fraction and prevention of left ventricular remodelling [59] (Fig. 2). A large and prospective community-based study revealed that lower serum 25-hydroxyvitamin D levels were associated with the risks of many chronic diseases [141]. Theofilis et al. reported that a lack of prior treatment with RAAS blockers and lower serum 25-hydroxyvitamin D levels were independently associated with elevated risks of death or dialysis dependence and that the 25-hydroxyvitamin D/parathyroid hormone ratio was the most precise indicator of the composite endpoint [140]. The changes in cardiometabolic, cardiorenal, and other biomarkers were the same in vitamin D-deficient black subjects and white subjects with CKD in the southern Sahara region. However, these aberrant changes are more acute in black subjects than in white subjects [142]. Oral 25-hydroxyvitamin D supplementation increased the estimated glomerular filtration rate, inhibited secondary hyperparathyroidism, reduced proteinuria levels, and decreased the risk of cardiac failure, including NT-proBNP and cardiac troponin T, which were accompanied by the suppression of RAAS activity [142]. In addition, cobalt protoporphyrin decreased the plasma levels of AngII and renin in MI model mice. However, stannous mesoporphyrin abrogated these improvements [113]. Therefore, targeting these RAS components could be considered a potential therapeutic strategy for the treatment of CRS.

Accumulating evidence has suggested that MRA has beneficial effects on decreasing heart failure-related hospitalisations and death in patients with heart failure with a preserved ejection fraction [143]. A recent study showed that eplerenone mitigated CKD and CVD progression by reducing blood pressure, blood sugar levels, sympathetic nerve excitation and cardiomyocyte hypertrophy in rats with CRS4-induced by NX [144]. However, eplerenone did not significantly affect tubulointerstitial lesions, glomerular damage, or aberrant cardiovascular function [144]. Similarly, a recent study showed that eplerenone ameliorated cardiac fibrosis in rats with CRS4-induced by unilateral ureteral obstruction (UUO) and the macrophage-to-myofibroblast transition [145]. Furthermore, in vitro experiments revealed that eplerenone suppressed the aldosterone-activated mineralocorticoid receptor-induced macrophage-to-myofibroblast transition and increased CTGF secretion from macrophages [145]. An earlier study showed that spironolactone and eplerenone exerted beneficial effects on patients with acute myocardial infarction and heart failure with an ejection fraction < 40% without advanced CKD [146]. In addition, spironolactone use upfront in patients with AHF at high risk of CRS is safe and increases

natriuresis [147]. However, olmesartan medoxomil decreased proteinuria and mononuclear cell infiltration in CRS2 rats, whereas spironolactone did not [148]. Taken together, these findings suggest that MRA is also an effective therapeutic strategy for the treatment of CRS.

Treatment of CRS by reshaping the gut microbiota

Increasing evidence has indicated that reshaping the gut microbiota has potential in the treatment of CRS [149]. Treatment with linaclotide, a guanylate cyclase C agonist, restored microbial dysbiosis in adenine-induced CKD mice [90] (Fig. 3). Compared with that in CKD mice, the microbial richness was significantly increased in CKD mice treated with linaclotide, which was accompanied by increased α diversity [90]. Further analysis revealed that the microbial composition of CKD mice differs from that of linaclotide-treated CKD mice [90]. The taxonomic analysis revealed that the relative abundances of Clostridiales and Dehalobacteriaceae were reduced in CKD mice treated with linaclotide [90]. Compared with that in CKD mice, the relative abundance of *Dehalobacterium* was reduced in CKD mice treated with linaclotide, which was accompanied by a decrease in the relative abundance of *Corynebacterium* among minor populations [90]. Using the metabolomic technique, the same research group reported that treatment with linaclotide led to decreased plasma levels of TMAO, indoxyl sulfate, hippurate, creatinine, urea and *trans*-aconitate in CKD mice [90] (Fig. 3). In choline-fed model mice, linaclotide decreased plasma TMAO levels but did not change the plasma levels of indoxyl sulfate or phenyl sulfate, causing the downregulation of proinflammatory and profibrotic mRNA expression and decreased levels of plasma cardiac fibrotic markers, including galectin-3 and ST2, indicating a cardioprotective effect [90]. Similar results were also observed after treatment with 3,3-dimethyl-1-butanol, a TMAO inhibitor, in NX- and MI-induced rats with CRS2 [98] (Fig. 3). Collectively, these publications suggest that reshaping microbial dysbiosis can improve CRS.

Treatment of CRS via the regulation of noncoding RNAs

The dysregulation of noncoding RNAs plays an important role in the development of CRS; thus, the development of treatment approaches highlights the necessity of regulating noncoding RNAs and gene expression to control this disease [101]. Early publications have shown that modulators of the miR-200 family upregulate S6K1 mRNA-related miRNAs to achieve the optimal effect of the mTOR/S6K1signalling pathway, which reduces cardiac insulin resistance without eliminating its downstream beneficial effects, such as AT_2R upregulation [106]. A recent study revealed that treatment with clofibrate, a PPARα agonist, inhibited the effect of miR-21-5p, followed by improving left ventricle function in NX-induced rats with CRS4 [45] (Fig. 4). Moreover, Lindoso et al. observed an attenuated miR-200-TGF-β axis through the downregulation of the expression of the miR-200 family and miR-155-5p and the upregulation of miR-200c-3p expression in CRS rats treated with extracellular vesicles [54] (Fig. 4). In addition to regulating miRNAs, *Panax notoginseng* saponins suppress cardiomyocyte pyroptosis by downregulating lncRNA ANRIL expression in hypoxia-induced H9c2 cells [111] (Fig. 4). Taken together, these findings show that regulating noncoding RNAs is a potential therapeutic strategy for the treatment of CRS.

CONCLUDING REMARKS AND PERSPECTIVES

CRS is considered a disease in which the dysfunction of cardiorenal crosstalk leads to coinjury of the heart and kidney with high morbidity and mortality. Early publications reported a variety of common mechanisms, such as haemodynamics, neurohormonal abnormalities, hypervolemia, hyperuraemia and hyperuricaemia. Traditional therapies for CRS improve haemodynamic and neurohormonal abnormalities, as well as patient-centred monitoring tools such as markers of hypertension, congestion and kidney function. Moreover, previous studies have focused on anaemia, cachexia and vitamin D deficiency, as well as aberrant iron metabolism. In this review, the classification and current diagnostic biomarkers of CRS are summarised. Furthermore, recent molecular mechanisms of CRS are highlighted, including classical pathogenic mechanisms, such as oxidative stress and inflammation; the hyperactive RAAS; the maladaptive Wnt/β-catenin signalling pathway; and the profibrotic TGF–β1/Smad signalling pathway; as well as novel pathogenic mechanisms, such as dysbiosis of the gut microbiota and dysregulation of noncoding RNAs. Because these signals are involved in CRS, various therapies that target them to exert therapeutic effects on CRS have been reported.

Notably, few effective treatments for CRS are available. Concurrently illuminating challenges and opportunities is a stepping stone for discovering novel treatment strategies for CRS. We believe that further accurate classification of CRS subtypes through the identification of early differential diagnostic biomarkers via multiomics techniques will provide novel approaches for the clinical diagnosis and prevention of CRS. Although some publications have described the dysbiosis of the gut microbiota and dysregulation of noncoding RNAs in CRS, studies of CRS are still in their infancy compared with those of cancer, diabetes and CVD. In addition, an improved understanding of the molecular mechanisms of the disease is needed for the rapid discovery of novel therapeutic agents and strategies. Therefore, combining interdisciplinary and joint diagnostic methods to elucidate new pathogenic pathways and identify therapeutic targets is urgently needed to decrease the morbidity and mortality of CRS in the future.

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ADDITIONAL INFORMATION

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